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Comparative Results of 327 Chemical Carcinogenicity Studies

by J. K. Haseman,* J. E. Huff,* E. Zeiger,* and E. E. McConnell*

The National Cancer Institute (NCI) and the National Toxicology Program (NTP) have carried out a number of laboratory animal carcinogenicity studies and presented the results of these experiments in a series of Technical Reports. This paper tabulates the results of the 327 NCI/NTP studies carried out to date on 308 distinct chemicals, and discusses certain issues relevant to the evaluation of carcinogenicity in these experiments. This compilation of results from NCI/NTP carcinogenicity experiments provides a large database that can be used to study structure-activity correlations, interspecies concordance, and associations between laboratory animal carcinogenicity and other toxicological effects.

Introduction

The National Cancer Institute (NCI) and the National Toxicology Program (NTP) have designed, carried out, and evaluated more than 300 long-term chemical carcinogenicity studies in laboratory rodents. The majority of these studies involve four sex-species experiments: male and female rats and mice. The strains most commonly used are Fischer 344 rats and B6C3F1 mice; other animals occasionally used include Osborne-Mendel and Sprague-Dawley rats, Syrian golden hamsters, and ICR Swiss, Swiss-Webster, and Swiss CD-1 mice. In most of these studies the chemical was administered for 2 years, although certain NCI mouse experiments were of a shorter duration. The results of these NCI/NTP studies have been presented in a series of Technical Reports (TRs), and in addition are often published in the scientific literature. These data are utilized by the international scientific community and by various government agencies in making regulatory decisions affecting public health. The objective of this paper is to provide a tabulated compilation of the results of these NCI/NTP laboratory animal carcinogenicity studies.

Several authors have abstracted and summarized results for certain subsets of these studies (*1–6*). Additional information regarding the design, analysis, and interpretation of these experiments is available (*7–9*). The carcinogenic potencies of chemicals evaluated by the NCI/NTP have also been estimated (*10,11*).

Materials and Methods

This compilation of results covers all chemicals studied for long-term toxicity and carcinogenicity by the NCI or by the NTP and reported in the Technical Report series. Included are all studies that have been approved by the NCI Clearinghouse or by the NTP Board of Scientific Counselors' Peer Review Panel (established in June, 1980) through June 1, 1987. A total of 327 studies (1237 individual sex-species experiments) have been evaluated, involving 308 distinct chemicals. Seventeen chemicals were studied twice (trichloroethylene three times) by different laboratories, in different species or strains, and/or by different routes of administration.

The numbering of the Technical Reports contains gaps that correspond to chemicals for which Technical Reports were originally intended but never issued. Also, certain Technical Report numbers were assigned to guidelines and other documents that do not report results of specific studies. Technical Reports that were not printed or do not present results of carcinogenicity studies include numbers 1, 44, 79, 87, 119, 167, 176, 182, 188, 218, 241, 254, and 258. Single copies of available Technical Reports may be obtained from the NTP (P.O. Box 12233, Research Triangle Park, NC 27709).

For experiments evaluated by the NCI or the NTP prior to in June, 1983, results are reported in this paper as "positive," "negative," "equivocal," or "inadequate." In June, 1983, the NTP adopted the use of "categories of evidence" (*12–14*), which were used to classify study results evaluated after that date. This approach places the result of each individual sex-species experiment into one of five categories: two correspond to positive results ("clear evidence" or "some evidence" of carcinogenicity), one is for uncertain findings ("equivocal evidence"), one is for negative studies ("no evidence"), and one is for studies that cannot be evaluated because of major flaws ("inadequate studies").

*National Institute of Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC 27709.

Table 1. NCI carcinogenicity results for 202 studies (781 experiments).

Chemical name	TR no.	Carcinogenicity result: Route	MR	FR	MM	FM
Acetohexamide	050	Feed	N	N	N	N
Acronycine	049	IP/LJ	P	P	I	I
Aldicarb	136	Feed	N	N	N	N
Aldrin	021	Feed	E[a]	E[a]	P	N
Allyl chloride	073	Gav	N	N	E	E
2-Aminoanthraquinone	144	Feed	P	I	P	P
3-Amino-4-ethoxyacetanilide	112	Feed	N	N	P	N
3-Amino-9-ethylcarbazole	093	Feed	P	P	P	P
1-Amino-2-methylanthraquinone	111	Feed	P	P	N	P
4-Amino-2-nitrophenol	094	Feed	P	E	N	N
2-Amino-5-nitrothiazole	053	Feed	P	N	N	N
Anilazine	104	Feed	N	N	N	N
Aniline hydrochloride	130	Feed	P	P	N	N
o-Anisidine hydrochloride	089	Feed	P	P	P	P
p-Anisidine hydrochloride	116	Feed	E	N	N	N
o-Anthranilic acid	036	Feed	N	N	N	N
Aroclor 1254	038	Feed	E	E	NT	NT
Aspirin, phenacetin, and caffeine	067	Feed	N[a]	E[a]	N	N
5-Azacytidine	042	IP/LJ	I	I	I	P
Azinphosmethyl	069	Feed	E	N	N	N
Azobenzene	154	Feed	P	P	N	N
Benzoin	204	Feed	N	N	N	N
1,2,3-Benzotriazole	088	Feed	E	E	N	E
Bis(2-chloro-1-methylethyl) ether	191	Gav	N	N	NT	NT
Butylated hydroxytoluene	150	Feed	N	N	N	N[a]
Calcium cyanamide	163	Feed	N	N	N	N
Captan	015	Feed	N	N	P[a]	P[a]
Carbromal	173	Feed	N	N	N	N
Chloramben	025	Feed	N	N	E	P
Chlordane (technical grade)	008	Feed	N[a]	N[a]	P	P
4-(Chloroacetyl)acetanilide	177	Feed	N	N	N	N
p-Chloroaniline	189	Feed	E	N	E	E
Chlorobenzilate	075	Feed	E	E	P	P
2-Chloroethyltrimethyl-ammonium chloride	158	Feed	N	N	N	N
2-Chloromethylpyridine hydrochloride	178	Gav	N	N	N	N
3-Chloromethylpyridine hydrochloride	095	Gav	P	E[a]	P	P
4-Chloro-*m*-phenylenediamine	085	Feed	P	N	N	P
4-Chloro-*o*-phenylenediamine	063	Feed	P	P	P	P
2-Chloro-*p*-phenylenediamine sulfate	113	Feed	N[a]	N[a]	N	N
Chloropicrin	065	Gav	I	I	N	N
Chlorothalonil	041	Feed	P	P	N	N
3-Chloro-*p*-toluidine	145	Feed	N	N	N	N
5-Chloro-*o*-toluidine	187	Feed	N	N	P	P
4-Chloro-*o*-toluidine hydrochloride	165	Feed	N	N	P	P
Chlorpropamide	045	Feed	N	N	N	N
C.I. direct black 38 (90-day study)	108	Feed	P	P	NT	NT
C.I. direct blue 6 (90-day study)	108	Feed	P	P	NT	NT
C.I. direct brown 95 (90-day study)	108	Feed	NT	P	NT	NT
C.I. vat yellow 4	134	Feed	N	N	P	N
Cinnamyl anthranilate	196	Feed	P	N	P	P
Clonitralid	091	Feed	N	E	I	N
Coumaphos	096	Feed	N	N	N	N

table continues

Table 1. *Continued*

Chemical name	TR no.	Carcinogenicity result: Route	MR	FR	MM	FM
m-Cresidine	105	Gav	P	P	I	N
p-Cresidine	142	Feed	P	P	P	P
Cupferron	100	Feed	P	P	P	P
2,4-Diaminoanisole sulfate	084	Feed	P	P	P	P
2,4-Diaminotoluene	162	Feed	P	P	N	P
Diarylanilide yellow	030	Feed	N	N	N	N
Diazinon	137	Feed	N	N	N	N
Dibenzo-*p*-dioxin	122	Feed	N	N	N	N
1,2-Dibromo-3-chloropropane	028	Gav	P	P	P	P
1,2-Dibromoethane (ethylene dibromide)	086	Gav	P	P	P	P
Dibutyltin diacetate	183	Feed	N	I	N	N[a]
2,7-Dichlorodibenzo-*p*-dioxin	123	Feed	N	N	E	N
Dichlorodiphenylethylene (*p,p'*-DDE)	131	Feed	N	N	P	P
Dichlorodiphenyltrichloroethane (*p,p'*-DDT)	131	Feed	N	N	N	N
1,1-Dichloroethane	066	Gav	N	E	N	E
1,2-Dichloroethane	055	Gav	P	P	P	P
Dichlorvos	010	Feed	N	N	N	N
Dicofol	090	Feed	N	N	P	N
N,N'-Dicyclohexylthiourea	056	Feed	N	N	N	N
Dieldrin	021	Feed	N	N	E[a]	N
Dieldrin	022	Feed	N	N	NT	NT
N,N'-Diethylthiourea	149	Feed	P	P	N	N
Dimethoate	004	Feed	N	N	N	N
2,4-Dimethoxyaniline hydrochloride	171	Feed	N	N	N	N
3,3'-Dimethoxybenzidine-4,4'-diisocyanate	128	Feed	P	P	N	N
Dimethyl terephthalate	121	Feed	N	N	E	N
2,4-Dinitrotoluene	054	Feed	P	P	N	N
1,4-Dioxane	080	Water	P	P	P	P
Dioxathion	125	Feed	N	N	N	N
2,5-Dithiobiurea	132	Feed	N	N	N	E
Emetine	043	IP/LJ	I	I	I	I
Endosulfan	062	Feed	I	N	I	N
Endrin	012	Feed	N	N	N	N
Estradiol mustard	059	Gav	N	N	P	P
Ethionamide	046	Feed	N	N	N	N
Ethylenediamine tetraacetic acid (EDTA)	011	Feed	N	N	N	N
p,p'-Ethyl-DDD	156	Feed	N	N	N	E
Ethyl tellurac	152	Feed	E[a]	N	E[a]	E[a]
Fenthion	103	Feed	N	N	E	N
Fluometuron	195	Feed	N	N	E	N
Formulated fenaminosulf	101	Feed	N	N	N	N
Heptachlor	009	Feed	N	E[a]	P	P
1,2,3,6,7,8-Hexachlorodibenzo-*p*-dioxin	198	Gav	E[a]	P	P	P
1,2,3,6,7,8-Hexachlorodibenzo-*p*-dioxin	202	SP	NT	NT	N	N
Hexachloroethane	068	Gav	N	N	P	P
Hexachlorophene	040	Feed	N	N	NT	NT
Hydrazobenzene	092	Feed	P	P	N	P
ICRF-159	078	IP/LJ	N	P	N	P
3,3'-Iminobis-1-propanol dimethanesulfonate HCl	018	IP/LJ	E[a]	E[a]	E[a]	E[a]
Iodoform	110	Gav	N	N	N	N
Isophosphamide	032	IP/LJ	N	P	N	P
Lasiocarpine	039	Feed	P	P	NT	NT
Lead dimethyldithiocarbamate	151	Feed	N	N	N	N

table continues

Table 1. *Continued*

Chemical name	TR no.	Route	Carcinogenicity result MR	FR	MM	FM
Lindane	014	Feed	N	N	N	N
Lithocholic acid	175	Gav	N	N	N	N
Malaoxon	135	Feed	N	N	N	N
Malathion	024	Feed	N	N	N	N
Malathion	192	Feed	N	N	NT	NT
DL-Menthol	098	Feed	N	N	N	N
Methoxychlor	035	Feed	N	N	N	N
4,4′-Methylenebis(*N*,*N*-dimethyl)benzenamine	186	Feed	P	P	E	P
2-Methyl-1-nitroanthraquinone	029	Feed	P	P	P	P
Methyl parathion	157	Feed	N	N	N	N
Mexacarbate	147	Feed	N	N	N	N
Michler's ketone	181	Feed	P	P	P	P
1,5-Naphthalenediamine	143	Feed	N	P	P	P
N-(1-Naphthyl) ethylenediamine dihydrochloride	168	Feed	N	N	N	N
Nithiazide	146	Feed	N	P	P	E[a]
Nitrilotriacetic acid (NTA)	006	Feed	P[a]	P	P	P[a]
Nitrilotriacetic acid, Na_3 H_2O (study 1)	006	Feed	E	E	N	N
Nitrilotriacetic acid, Na_3 H_2O (study 2)	006	Feed	P	P	NT	NT
5-Nitroacenaphthene	118	Feed	P	P	N	P
3-Nitro-*p*-acetophenetide	133	Feed	N	N	P	N
5-Nitro-*o*-anisidine	127	Feed	P	P	E[a]	P
4-Nitroanthranilic acid	109	Feed	N	N	N	N
6-Nitrobenzimidazole	117	Feed	N	N	P	P
Nitrofen	026	Feed	I	P	P	P
Nitrofen	184	Feed	N	N	P	P
1-Nitronaphthalene	064	Feed	N	N	N	N
2-Nitro-*p*-phenylenediamine	169	Feed	N	N	N	P
4-Nitro-*o*-phenylenediamine	180	Feed	N	N	N	N
3-Nitropropionic acid	052	Gav	E	N	N	N
N-Nitrosodiphenylamine	164	Feed	P	P	N	N
p-Nitrosodiphenylamine	190	Feed	P	N	P	N
β-Nitrostyrene	170	Gav	N	N	N[a]	N
5-Nitro-*o*-toluidine	107	Feed	N	N	P	P
4,4′-Oxydianiline	205	Feed	P	P	P	P
Parathion	070	Feed	E	E	N	N
Pentachloronitrobenzene	061	Feed	N	N	N	N
Phenazopyridine hydrochloride	099	Feed	P	P	N	P
Phenesterin	060	Gav	N	P	P	P
Phenformin	007	Feed	N	N	N	N
Phenol	203	Water	N	N	N	N
Phenoxybenzamine hydrochloride	072	IP/LJ	P	P	P	P
p-Phenylenediamine dihydrochloride	174	Feed	N	N	N	N
1-Phenyl-3-methyl-5-pyrazolone	141	Feed	N	N	N	N
N-Phenyl-*p*-phenylenediamine	082	Feed	N	N	N	N
1-Phenyl-2-thiourea	148	Feed	N	N	N	N
Phosphamidon	016	Feed	E[a]	E[a]	N	N
Photodieldrin	017	Feed	N	N	N	N
Phthalamide	161	Feed	N	N	N	N
Phthalic anhydride	159	Feed	N	N	N	N
Picloram	023	Feed	N	E	N	N
Piperonyl butoxide	120	Feed	N	N	N	N
Piperonyl sulfoxide	124	Feed	N	N	P	N

table continues

Table 1. *Continued*

Chemical name	TR no.	Route	Carcinogenicity result MR	FR	MM	FM
Pivalolactone	140	Gav	P	P	N	N
Procarbazine hydrochloride	019	IP/LJ	P	P	P	P
Proflavin	005	Feed	E[a]	N	E[a]	E[a]
Pyrazinamide	048	Feed	N	N	N	I
Pyrimethamine	077	Feed	N	N	I	N
p-Quinone dioxime	179	Feed	N	P	N	N
Reserpine	193	Feed	P	N	P	P
Selenium sulfide	194	Gav	P	P	N	P
Selenium sulfide	197	SP	NT	NT	N	N
Selsun	199	SP	NT	NT	N	N
Sodium diethyl-dithiocarbamate	172	Feed	N	N	N	N
Styrene	185	Gav	N	N	E	N
Succinic acid 2,2-dimethylhydrazide (diaminozide)	083	Feed	N	P	E	N
Sulfallate	115	Feed	P	P	P	P
Sulfisoxazole	138	Gav	N	N	N	N
3-Sulfolene	102	Gav	N	N	N	N
4,4′-Sulfonyldianiline (dapsone)	020	Feed	P	N	N	N
Tetrachlorodiphenylethane	131	Feed	E	N	N	N
1,1,2,2-Tetrachloroethane	027	Gav	E[a]	N	P	P
Tetrachloroethylene	013	Gav	I	I	P	P
2,3,5,6-Tetrachloro-4-nitroanisole	114	Feed	N	N	N	N
Tetrachlorvinphos	033	Feed	N	P[a]	P	P[a]
Tetraethylthiuram disulfide	166	Feed	N	N	N	N
4,4′-Thiodianiline	047	Feed	P	P	P	P
β-Thioguanidine deoxyriboside	057	IP/LJ	E	P	I	I
Titanium dioxide	097	Feed	N	N	N	N
Tolazamide	051	Feed	N	N	N	N
Tolbutamide	031	Feed	N	N	N	N
2,6-Toluenediamine dihydrochloride	200	Feed	N	N	N	N
2,5-Toluenediamine sulfate	126	Feed	N	N	N	N
o-Toluidine hydrochloride	153	Feed	P	P	P	P
Toxaphene	037	Feed	E	E	P	P
1,1,1-Trichloroethane (methyl chloroform)	003	Gav	I	I	I	I
1,1,2-Trichloroethane	074	Gav	N	N	P	P
Trichloroethylene	002	Gav	N	N	P	P
Trichlorofluoromethane	106	Gav	I	I	N	N
2,4,6-Trichlorophenol	155	Feed	P	N	P	P
Trifluralin	034	Feed	N	N	N	P
2,4,5-Trimethylaniline	160	Feed	P	P	E[a]	P
Trimethylphosphate	081	Gav	P[a]	N	N	P
Trimethylthiourea	129	Feed	N	P	N	N
Triphenyltin hydroxide	139	Feed	N	N	N	N
Tris(1-aziridinyl)phosphine sulfide (thio-tepa)	058	IP/LJ	P	P	P	P
Tris(2,3-dibromopropyl) phosphate	076	Feed	P	P	P	P
L-Tryptophan	071	Feed	N	N	N	N

[a] These experiments were particularly difficult to evaluate based on the wording in the technical report summaries.

Gav: gavage; IP/LJ: intraperitoneal injection; SP: skin painting.

P: positive for carcinogenicity; N: negative for carcinogenicity; E: equivocal for carcinogenicity; I: inadequate study; NT: not tested in long-term study; MR: male rats; FR: female rats; MM: male mice; FM: female mice.

We did not attempt to reclassify the earlier experiments in terms of these categories. A chemical was considered to be a carcinogen if it produced a carcinogenic response in at least one sex-species group. Carcinogenicity results are reported separately for the 202 studies evaluated by the NCI (Table 1) and the 125 evaluated by NTP (Table 2).

Results

Of the 1237 individual sex-species experiments, 381 (31%) were judged positive, 699 (57%) negative, 103 (8%) equivocal, and 54 (4%) were considered to be inadequate. There was little apparent difference in the incidences of positive results between males and females or between rats and mice: 32% (100/311) of the experiments in male rats (MR) were positive compared with 29% (89/312) in female rats (FR), 29% (88/303) in male mice (MM), and 34% (104/303) in female mice (FM). Six experiments in hamsters produced negative results, and two experiments in hamsters were considered inadequate for evaluation.

Of the 327 studies, 49% (159/327) resulted in a carcinogenic effect in at least one sex-species group; for 13% (42/327), the evidence of carcinogenicity was equivocal; 37% (120/327) showed no evidence of carcinogenicity, and 2% (6/327) were considered inadequate for evaluation. These latter six studies were combination studies of intermediate-range chrysotile asbestos and dimethylhydrazine (DMH) in hamsters (TR 246) and in rats (TR 295), a combination study of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin and DMBA (TR 201), and three single chemical studies: emetine (TR 43); 1,1,1-trichloroethane (TR 3); and trichloroethylene in four strains of rats (TR 273).

The distribution of carcinogenicity results was similar in NCI and NTP studies. Among the NCI carcinogenicity studies (Table 1), 47% (95/202) were positive, 39% (79/202) negative, 13% (26/202) equivocal, and 1% (2/202) inadequate. The corresponding proportions for the NTP studies (Table 2) were 51% (64/125) positive, 33% (41/125) negative, 13% (16/125) equivocal and 3% (4/125) inadequate.

Of the 120 studies showing no chemically induced neoplasia, 95 were judged negative in all four sex-species groups, 3 were negative in three groups (the fourth being inadequate), 4 were negative in two groups (with two inadequate experiments), and 18 were studied in one species and found to be noncarcinogenic in both sexes.

Of the 159 studies with carcinogenic effects, 38 were positive in all four sex-species groups, 24 were carcinogenic in three, 60 were carcinogenic in two (including 9 that were studied in one species), and 37 were positive in one sex-species group. Only 14 of the 37 "one-sex-species-positive" chemicals were negative in the other three sex species groups: 17 showed equivocal effects in at least one of the other groups; 4 were inadequately studied in at least one of the other groups; and the remaining 2 were studied in one species.

Table 2. NTP carcinogenicity results for 125 studies (456 experiments).

Chemical name	TR no.	Carcinogenicity result				
		Route	MR	FR	MM	FM
Agar	230	Feed	N	N	N	N
Allyl isothiocyanate	234	Gav	P	E	N	N
Allyl isovalerate	253	Gav	P	N	N	P
2-Amino-5-nitrophenol	334	Gav	SE	NE	NE	NE
11-Aminoundecanoic acid	216	Feed	P	N	E[a]	N
Ampicillin trihydrate	318	Gav	EE	NE	NE	NE
Asbestos, amosite	279	Feed	N	N	NT	NT
Asbestos, amosite (hamsters)	249	Feed	N	N		
Asbestos, intermediate-range (IR) chrysotile	295	Feed	SE	NE	NT	NT
Asbestos, IR chrysotile (hamsters)	246	Feed	N	N		
Asbestos, IR chrysotile + DMH (hamsters)	246	Feed	IS	IS		
Asbestos, IR chrysotile + DMH	295	Feed	IS	IS	NT	NT
Asbestos, short-range (SR) chrysotile	295	Feed	NE	NE	NT	NT
Asbestos, SR chrysotile (hamsters)	246	Feed	N	N		
Asbestos, crocidolite	280	Feed	N	N	NT	NT
Asbestos, tremolite	277	Feed	N	N	NT	NT
L-Ascorbic acid	247	Feed	N	N	N	N
Benzene	289	Gav	CE	CE	CE	CE
Benzyl acetate	250	Gav	E[a]	N	P	P
2-Biphenylamine hydrochloride	233	Feed	N	N	E	P
Bis(2-chloro-1-methylethyl) ether	239	Gav	NT	NT	P	P
Bisphenol A	215	Feed	E[a]	N	N	N
Boric acid	324	Feed	NT	NT	NE	NE
Bromodichloromethane	321	Gav	CE	CE	CE	CE
1,3-Butadiene	288	Inhal	NT	NT	CE	CE
Butyl benzyl phthalate	213	Feed	I	P[a]	N	N
n-Butyl chloride	312	Gav	NE	NE	NE	NE
Caprolactam	214	Feed	N	N	N	N
Chlorendic acid	304	Feed	CE	CE	CE	NE
Chlorinated paraffins: C12, 60% chlorine	308	Gav	CE	CE	CE	CE
Chlorinated paraffins: C23, 43% chlorine	305	Gav	NE	EE	CE	EE
Chlorinated trisodium phosphate	294	Gav	IS	IS	NE	NE
Chlorobenzene	261	Gav	E[a]	N	N	N
Chlorodibromomethane	282	Gav	NE	NE	EE	SE
2-Chloroethanol (ethylene chlorohydrin)	275	SP	NE	NE	NE	NE
3-Chloro-2-methylpropene	300	Gav	CE	CE	CE	CE
Chlorpheniramine maleate	317	Gav	NE	NE	NE	NE
C.I. acid orange 10	211	Feed	N	N	N	N
C.I. acid red 14	220	Feed	N	N	N	N
C.I. acid yellow 73 (fluorescein sodium)	265	Water	EE	NE	NE	NE
C.I. basic red 9 monohydrochloride	285	Feed	CE	CE	CE	CE
C.I. disperse blue 1	299	Feed	CE	CE	EE	NE
C.I. disperse yellow 3	222	Feed	P	N	N	P
C.I. solvent yellow 14	226	Feed	P	P	N	N

table continues

Table 2. *Continued*

Chemical name	TR no.	Carcinogenicity result				
		Route	MR	FR	MM	FM
Cytembena	207	IP/LJ	P	P	N	N
D & C red 9	225	Feed	P	E[a]	N	N
Decabromodiphenyl oxide	309	Feed	SE	SE	EE	NE
Diallyl phthalate	242	Gav	NT	NT	E	E[a]
Diallyl phthalate	284	Gav	NE	EE	NT	NT
1,2-Dibromo-3-chloro-propane	206	Inhal	P	P	P	P
1,2-Dibromoethane (ethylene dibromide)	210	Inhal	P	P	P	P
1,2-Dichlorobenzene (*o*-dichlorobenzene)	255	Gav	N	N	N	N
1,4-Dichlorobenzene	319	Gav	CE	NE	CE	CE
Dichloromethane (methylene chloride)	306	Inhal	SE	CE	CE	CE
2,6-Dichloro-*p*-phenylenediamine	219	Feed	N	N	P	P
1,2-Dichloropropane (propylene dichloride)	263	Gav	NE	EE	SE	SE
1,3-Dichloropropene (Telone II)	269	Gav	CE	SE	IS	CE
Diesel fuel marine	310	SP	NT	NT	EE	EE
Di(2-ethylhexyl)adipate	212	Feed	N	N	P	P
Di(2-ethylhexyl)phthalate	217	Feed	P	P	P	P
Diglycidyl resorcinol ether (DGRE)	257	Gav	P	P	P	P
Dimethyl hydrogen phosphite	287	Gav	CE	EE	NE	NE
Dimethyl methylphosphonate	323	Gav	SE	NE	IS	NE
Dimethyl morpholinophosphoramidate	298	Gav	SE	SE	NE	NE
Dimethylvinyl chloride (DMVC)	316	Gav	CE	CE	CE	CE
Ephedrine sulfate	307	Feed	NE	NE	NE	NE
1,2-Epoxybutane	329	Inhal	CE	EE	NE	NE
Ethoxylated dodecyl alcohol	264	Feed	N	N	N	N
Ethyl acrylate	259	Gav	P	P	P	P
Ethylene oxide	326	Inhal	NT	NT	CE	CE
Eugenol	223	Feed	N	N	E	E
FD & C yellow no. 6	208	Feed	N	N	N	N
Geranyl acetate	252	Gav	N	N	N	N
Gilsonite	270	Feed	NE	NE	NE	NE
Guar gum	229	Feed	N	N	N	N
Gum arabic	227	Feed	N	N	N	N
Hamamelis water (witch hazel)	286	SP	NE	NE	NE	NE
HC blue 1	271	Feed	EE	SE	CE	CE
HC blue 2	293	Feed	NE	NE	NE	NE
HC red 3	281	Gav	NE	NE	EE	IS
4-Hexylresorcinol	330	Gav	NE	NE	EE	NE
8-Hydroxyquinoline	276	Feed	NE	NE	NE	NE
Isophorone	291	Gav	SE	NE	EE	NE
Locust bean gum	221	Feed	N	N	N	N
Malonaldehyde, sodium	331	Gav	CE	CE	NE	NE
D-Mannitol	236	Feed	N	N	N	N
Melamine	245	Feed	P	N	N	N
2-Mercaptobenzothiazole	332	Gav	SE	SE	NE	EE
Methyl carbamate	328	Gav	CE	CE	NE	NE
4,4′-Methylenedianiline dihydrochloride	248	Water	P	P	P	P

table continues

Table 2. *Continued*

Chemical name	TR no.	Carcinogenicity result				
		Route	MR	FR	MM	FM
Methyl methacrylate	314	Inhal	NE	NE	NE	NE
Mirex	313	Feed	CE	CE	NT	NT
Monuron	266	Feed	CE	NE	NE	NE
Navy fuels JP-5	310	SP	NT	NT	NE	NE
Oxytetracycline hydrochloride	315	Feed	EE	EE	NE	NE
Pentachloroethane	232	Gav	E[a]	N	P	P
Pentachloronitrobenzene	325	Feed	NT	NT	NE	NE
Phenylephrine hydrochloride	322	Feed	NE	NE	NE	NE
N-Phenyl-2-naphthylamine	333	Feed	NE	NE	NE	EE
o-Phenylphenol	301	SP	NT	NT	NE	NE
Polybrominated biphenyls (Firemaster FF-1)	244	Gav	P	P	P	P
Propylene	272	Inhal	NE	NE	NE	NE
Propylene oxide	267	Inhal	SE	SE	CE	CE
Propyl gallate	240	Feed	E[a]	N	E[a]	N
Rotenone	320	Feed	EE	NE	NE	NE
Sodium (2-ethylhexyl)alcohol sulfate	256	Feed	N	N	N	E
Stannous chloride	231	Feed	E[a]	N	N	N
Tara gum	224	Feed	N	N	N	N
2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	209	Gav	P	P	P	P
2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	201	SP	NT	NT	E[a]	P
2,3,7,8-Tetrachlorodibenzo-*p*-dioxin + DMBA	201	SP	NT	NT	IS	IS
1,1,1,2-Tetrachloroethane	237	Gav	E[a]	N	P	P
Tetrachloroethylene	311	Inhal	CE	SE	CE	CE
Tetrakis (hydroxymethyl) phosphonium sulfate	296	Gav	NE	NE	NE	NE
Tetrakis (hydroxymethyl) phosphonium chloride	296	Gav	NE	NE	NE	NE
2,4- and 2,6-Toluene diisocyanate	251	Gav	P	P	N	P
Trichloroethylene (without epichlorohydrin)	243	Gav	I	N	P	P
Trichloroethylene	273	Gav	IS[b]	IS[b]	NT	NT
Tris(2-ethylhexyl)phosphate	274	Gav	EE	NE	NE	SE
4-Vinylcyclohexene	303	Gav	IS	IS	IS	CE
Vinylidene chloride	228	Gav	N	N	N	N
Xylenes (mixed)	327	Gav	NE	NE	NE	NE
2,6-Xylidine	278	Feed	P	P	NT	NT
Zearalenone	235	Feed	N	N	P	P
Ziram	238	Feed	P	N	N	E[a]

[a] These experiments were particularly difficult to evaluate based on the wording in the technical report summaries.

[b] Experiments in four strains of rats considered inadequate.

Gav: gavage; IP/LJ: intraperitoneal injection; Inhal: inhalation; SP: skin painting.

For studies evaluated prior to categories of evidence, P: positive for carcinogenicity; N: negative for carcinogenicity; E: equivocal for carcinogenicity; I: inadequate study; NT: not tested in long-term study. For studies using categories of evidence, CE: clear evidence of carcinogenicity; SE: some evidence of carcinogenicity; EE: equivocal evidence of carcinogenicity; NE: no evidence of carcinogenicity; IS: inadequate study of carcinogenicity; NT: not tested in long-term study; MR: male rats; FR: female rats; MM: male mice; FM: female mice.

Rats and mice showed a high concordance with regard to carcinogenicity outcome. This association is summarized in Table 3 for the 266 chemicals that were adequately studied in both sexes of both species. The concordance in response between rats and mice (with equivocal results considered negative) was 75% (138/183) for feeding studies, 66% (41/62) for gavage studies and 90% (19/21) for all other routes of administration.

If equivocal studies are considered negative, then 67 chemicals showed carcinogenic effects in a least one sex of both species; 131 chemicals showed no carcinogenic effects in any of the four sex-species groups; 32 chemicals were carcinogenic in rats (males, females, or both) but not in mice; and 36 were carcinogenic in mice but not in rats. As shown in Table 3, the concordance among species is similar, regardless of how the equivocal study results are considered.

If individual sex-species groups are compared, then the overall concordance in carcinogenic response between sexes is quite high for both rats (255/292, 87%) and mice (255/288, 89%). For the four interspecies comparisons, the lowest concordance is that observed between male rats and male mice (191/270, 71%), the highest concordance is between female rats and female mice (213/275, 77%).

The interspecies concordance in carcinogenic response for the NCI/NTP studies is similar to that reported by Purchase (*15*) in a literature-based evaluation of 250 carcinogenicity experiments (which included some of the NCI studies considered in our analysis). He reported 82% concordance among rats and mice: 38% of the chemicals were not carcinogenic in either species, and 44% were carcinogenic in both species.

Discussion

Although we present a list of conclusions regarding the carcinogenicity of a series of chemicals in rats and mice as positive, negative, equivocal, or inadequate, we recognize that these are categories whose boundaries are not clearly defined. These categories are designed to encompass a spectrum of responses because each carcinogenesis study produces a unique set of results. While these categories are useful in providing a general indication of a chemical's carcinogenicity, as well as providing a certain comparability across studies, they should never be used as a substitute for a more detailed evaluation of the study design, data analysis, and results as presented in the Technical Reports.

Table 3. Concordance of carcinogenicity outcome between rats and mice.

	Equivocal results excluded		Equivocal results considered positive		Equivocal results considered negative	
	Rats +	Rats −	Rats +	Rats −	Rats +	Rats −
Mice +	67	25	92	38	67	36
Mice −	25	95	41	95	32	131
Concordance	76% (162/212)		70% (187/266)		74% (198/266)	

While the reader is encouraged to consult the full Technical Report for more detailed evaluations, it must also be kept in mind that there have been significant advances in chemical carcinogenesis in recent years. These include increased knowledge about specific organ or tissue tumor responses, more refined and uniform histopathologic diagnoses, use of survival-adjusted statistical methods, extensive data on historical control tumor incidences, and increased understanding of biological/toxicological mechanisms of chemically induced neoplasia. These factors all have an impact on current evaluations of experimental results.

For the majority of the NCI/NTP studies, the summary conclusions given in the Technical Reports were unambiguous. In some cases the particular wording used for the conclusion made it difficult to place a result in the most appropriate classification in terms of "positive," "negative," or "equivocal." Perhaps for these reasons, previous summaries (*1–3*) of certain of these carcinogenicity studies are not in complete agreement regarding the overall interpretation of experimental results.

We have indicated by a superscript in Tables 1 and 2 those experimental results that were considered to be particularly difficult to classify based on the wording of the Technical Report summaries. For example, for some chemicals the conclusion in the Technical Report was "not carcinogenic," but to this evaluation was added the notation that increased incidences of certain tumors "may have been related to" or "may have been associated with" chemical exposure. One interpretation could be that the intended conclusion was "negative," and that the additional information was provided to indicate effects that had been considered, but perhaps discounted as not being biologically important. Another interpretation could be that the intended conclusion was "not positive," and that the additional information was provided to convey findings that were considered "less than positive," but not fully negative, i.e., "equivocal." In our evaluation, the latter interpretation was adopted. Chemicals for which this type of language was used in the Technical Reports included 11-aminoundecanoic acid (MM), D & C red 9 (FR), dieldrin (MM), ethyl tellurac (MR, MM, FM), propyl gallate (MR, MM), stannous chloride (MR), 1,1,1,2-tetrachloroethane (MR), and the dermal study of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (MM).

For example, previously published evaluations of dieldrin exposure to male mice (based on the data in NCI Technical Report 21) range from no evidence of carcinogenicity (*3*) to evidence suggestive of a carcinogenic effect (*1*) to carcinogenic (*2*). NCI Technical Report 21 concluded that an increased incidence of hepatocellular carcinoma "may be associated with treatment," and we regarded this as an equivocal response (Table 1). For the tabulated results given in Tables 1 and 2, we relied upon the conclusions given in the individual Technical Reports, but we recognize that in some instances alternative interpretations of these conclusions are possible.

Approximately 50% of all chemicals evaluated for carcinogenicity in rodents by the NCI/NTP gave positive results in at least one sex-species group. This agrees with earlier findings (*3,4*). However, this percentage may be misleading, as it does not differentiate between a chemical producing a single-site carcinogenic response in only one sex-species group and a chemical showing multiple organ effects in all four sex-species experiments.

Thus, a weight of the evidence approach must be used when considering potential hazards to humans. For example, the 38 chemicals that were positive in all four sex-species groups should perhaps receive the highest priority with regard to comprehensive epidemiologic studies, as well as increased public health consciousness. Again, the full experimental results on a chemical must be considered and evaluated before deciding on a course of public health action.

The concordance in carcinogenic response found between rats and mice in the NCI/NTP data was 74%. Despite this high concordance, however, we believe that both sexes of two rodent species should continue to be used, in most studies, to determine the long-term toxicology and carcinogenesis effects of chemical exposures. Although some investigators feel that this high concordance implies that the mouse is redundant and should not be used in determining the carcinogenicity of chemicals (*16*), most national and international scientific guidelines for laboratory animal carcinogenicity studies (*17–19*) recommend that at least two species be used. Further, for the NCI/NTP studies the similarity in carcinogenic response between sexes within a species was greater than the redundancy across species.

We are hopeful that this tabulation of chemical carcinogenesis results from all NCI/NTP studies carried out to-date will stimulate more in depth review of the actual data in the NCI/NTP Technical Reports that led to the abbreviated results shown in Tables 1 and 2.

REFERENCES

1. Chu, K. C., Cueto, C., and Ward, J. M. Factors in the evaluation of 200 National Cancer Institute carcinogen bioassays. J. Toxicol. Environ. Health 8: 251–280 (1981).
2. DiCarlo, F. J., and Fung, V. A. Summary of carcinogenicity data generated by the National Cancer Institute/National Toxicology Program. Drug Metab. Rev. 15(5,6): 1251–1273 (1984).
3. Griesemer, R. A., and Cueto, C. Toward a classification scheme for degrees of experimental evidence for the carcinogenicity of chemicals for animals. In: Molecular and Cellular Aspects of Carcinogen Screening Tests (R. Montesano, H. Bartsch, and L. Tomatis, Eds.), IARC Scientific Publications No. 27, Lyon, 1980, pp. 259–281.
4. Haseman, J. K., Crawford, D. D., Huff, J. E., Boorman, G. A., and McConnell, E. E. Results from 86 two-year carcinogenicity studies conducted by the National Toxicology Program. J. Toxicol. Environ. Health. 14: 621–639 (1984).
5. Maronpot, R. R., Haseman, J. K., Boorman, G A., Eustis, S. E., Rao, G. N., and Huff, J. E. Liver lesions in B6C3F1 mice: The National Toxicology Program experience and position. Arch. Toxicol. (Suppl.) 10: 10–26 (1987).
6. Huff, J. E., McConnell, E. E., Haseman, J. K., Boorman, G. A., Eustis, S. L., Schwetz, B. A., Rao, G. N., Jameson, C. W., Hart, L. G., and Rall, D. P. Carcinogenesis studies: results of 398 experiments on 104 chemicals from the U.S. National Toxicology Program. Annuals of the New York Academy of Sciences (Proceedings of the Collegium Ramazzini Conference on Living in a Chemical World, Bologna, Italy, October 6–10, 1985), in press.
7. Sontag, J. M., Page, N. P., and Safiotti, U. Guidelines for Carcinogen Bioassay in Small Rodents. DHHS Publication (NIH) 76-801, National Cancer Institute, Bethesda, MD, 1976.
8. Huff, J. E., Moore, J. A., Haseman, J. K., and McConnell, E. E. The National Toxicology Program, toxicology data evaluation techniques, and long-term carcinogenesis studies. In: Safety Evaluation of Drugs and Chemicals (W. E. Lloyd, Ed.), Hemisphere Publishing Corporation, Washington, DC, 1986, pp. 411–447.
9. Haseman, J. K. Statistical issues in the design, analysis and interpretation of animal carcinogenicity studies. Environ. Health Perspect. 58: 385–392 (1984).
10. Gold, L. S., Sawyer, C. B., Magaw, R., Backman, G. M., de Veciana, M., Levinson, R., Hooper, N. K., Havender, W. R., Bernstein, L., Peto, R., Pike, M. C., and Ames, B. N. Carcinogenic potency database of the standardized results of animal bioassays. Environ. Health Perspect. 58: 9–319 (1984).
11. Gold, L. S., de Veciana, M., Backman, G. M., Magaw, R., Lopipero, P., Smith, M., Blumenthal, M., Levinson, R., Bernstein, L., and Ames, B. N. Chronological supplement to the carcinogenic potency database: standardized results of animal bioassays published through December 1982. Environ. Health Perspect. 67: 161–200 (1986).
12. Huff, J. E., and Moore, J. A. Carcinogenesis studies design and experimental data interpretation/evaluation at the National Toxicology Program. In: Industrial Hazards of Plastics and Synthetic Elastomers (J. Jarvisalo, P. Pfaffli, and H. Vainio, Eds.), Alan R. Liss, Inc., New York, 1984, pp. 43–64.
13. National Toxicology Program. Fiscal Year 1984 Annual Plan. U.S. Department of Health and Human Services, Public Health Service, Research Triangle Park, NC 1984.
14. Rall, D. P. National Toxicology Program (NTP): Levels of evidence of carcinogenicity used to describe evaluative conclusions for long-term toxicology and carcinogenesis studies; request for comments. Federal Register. January 17, 1986. 51: 2579–2582.
15. Purchase, I. F. H. Inter-species comparisons of carcinogenicity. Br. J. Cancer 41: 454–468 (1980).
16. Schach von Wittenau, M., and Estes, P. C. The redundancy of mouse carcinogenicity bioassays. Fundam. Appl. Toxicol. 3: 631–639 (1983).
17. Board of Scientific Counselors, National Toxicology Program. Report of the NTP Ad Hoc Panel on Chemical Carcinogenesis Testing and Evaluation. U.S. Department of Health and Human Services, Public Health Service, Research Triangle Park, NC, August 17, 1984.
18. International Agency for Research on Cancer (IARC). Long-term and short-term screening assays for carcinogens: a critical appraisal. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Supplement 2, IARC, Lyon, 1980.
19. Office of Science and Technology Policy. Chemical carcinogens: a review of the science and its associated principles. Federal Register, March 14, 1985, 10371–10442.